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Possible Contribution from Epidemiological Studies

by E. Cuyler Hammond,* Wei-cheng You† and Long-de Wang‡

The problem of chemically contaminated water supplies are in general terms followed by a description of three examples of water supply problems in China. A large-scale prospective epidemiological study, now in the early planning stages, to be carried out in China is also described.

General Concerns Regarding Chemically Contaminated Water Supplies

Every so often, we run into a situation where a water supply is so heavily contaminated with some toxic chemical or mixture of chemicals that it is projected that a large number of exposed individuals will die or become ill as a consequence. That is amenable to epidemiological investigation, most readily so if illness becomes manifest within a short time after onset of exposure and resultant disease. As is typical of exposure to carcinogenic agents, the problem becomes more difficult, and valid answers cannot be obtained until a lapsed time of perhaps 20 or 30 years from the initial event. Whether the lapsed time is short or long, the problem is usually complicated by multiple types of exposures, multiple modes of exposure and other confounding factors. In situations where water is heavily contaminated with one chemical, it is likely also to be contaminated with other possibly harmful chemicals, and the air and/or food may be contaminated as well. Further, there may be unrelated confounding variables. For example, the exposed subjects may be unusually heavy smokers or they may be Cantonese who are at high risk of nasopharyngeal cancer.

The best way to resolve these difficulties is to study various groups that have been heavily exposed to a chemical in question but differ in respect to other exposures. For example, asbestos insulation workers are exposed to dust from other insulating material, but not so for asbestos cloth weavers. Some asbestos workers smoke cigarettes while others do not. Convincing evidence that occupational exposure to asbestos greatly increases the risk of lung cancer and mesothelioma comes from a set of studies which shows that both in the presence and in the absence of other occupational exposure, and with smoking habits being taken into consideration, occupational exposure to asbestos dust is associated with greatly increased risk of these two diseases. While this example involves inhalation, rather than ingestion, it illustrates the necessity of multiple epidemiological investigations.

Obviously we are concerned about extreme exposure; but from the standpoint of public health, lighter exposure of very large numbers of people may be far more important. As exposure decreases, the frequency and/or severity of resulting illness decreases; the number of subjects required for valid investigation increases greatly; and the problem of confounding variables becomes far more important and difficult to handle. Generally, the effect of lesser exposure is investigated only when suggested by epidemiological or experimental findings

*The Mount Sinai School of Medicine of the City University of New York, New York, NY 10029.
†Peking Institute for Cancer Research, Peking, China.
‡Cancer Institute of Chinese Academy of Medical Sciences.

in groups of human beings or animals that have been exposed at relatively very high dosage.

There is a temptation to argue in simple fashion from extremes "if much is bad, then half as much is probably half as bad." Unfortunately, in some emergency situations, there is little else we can do except to act on the assumption that if very much is very bad, then even a trace may be harmful. There is no quarrel with this as a temporary expediency when it is feasible.

The difficulty is that, except for a few toxic chemicals which have been extensively studied, we have little or no knowledge of the shape of the dose–response curves for human beings. The dose–response curve is all-important, since, for effective control, we must set upper limits of allowable degree of contamination of water supplies.

Available evidence suggests that for chemical carcinogens, at doses which range from fairly low to extremely high, the dose–response curve approximates a straight line. We have virtually no direct evidence on the shape of the curve at far lower dosages. However, many investigators have expressed the opinion that any dose above zero probably carries above zero risk of cancer. If this is so, the curve is almost certainly not a continuous straight line over the entire possible range of dosage. The lower portion (starting at point 0,0) probably resembles a straight line with an extremely shallow slope. (Halving dosage in this range would result in only a slight reduction in risk; in this range, a dose–response relationship would be hard to prove.)

It seems safe to say that ascertaining the risk (if any) from relatively low levels of each of many types of water contamination is one of the most difficult problems which scientists have been called upon to tackle. In my opinion, the only feasible epidemiologic approach is to study the problem in each of many different locations where people are exposed to water containing specific chemical contaminants ranging in amounts from extremely low to extremely high. Very large numbers of subjects are required except in locations where contamination is extreme; and many variables must be taken into consideration. Such a project calls for international cooperation on a large scale.

An example is the situation in which the Canadian health department requested our laboratory to investigate serious damage to cattle, vegetables, trees and wildlife by fluoride emissions from a nearby plant. Exposure was apparently by both inhalation and ingestion over a period of years. The question was whether human health was impaired, and if so whether a dose–response relationship could be established. Small amounts of fluoride in drinking water reduces the risk of dental carries in children. The best evidence on harmful effects in human beings has come from studies in areas of India and China, where drinking water is heavily contaminated with fluorides and a large proportion of the inhabitants suffer severe bone damage. The concentration at which the net effect changes from harmful to beneficial is not known. Therefore, this is an important question in many countries, especially the United States and Canada where fluoridation of water is a common practice.

Our colleagues in Ottawa, who have considerable knowledge of the matter, are working with us and we have requested our Chinese colleagues to carry out extension studies in China. They have agreed to do so. China is ideal for such investigation because millions of people live in areas where the fluorine content of water is extraordinarily high, and other millions live in areas where the content is moderately high, moderate, low and very low. The prospective epidemiological study to be described will provide the necessary exposures and medical data.

Water Supply and Disease in China

China is an enormous country. The over 1 billion inhabitants are of 50 different ethnic groups; there is tremendous diversity of environmental conditions, and death rates from cancer of various sites vary greatly from one province to another. It is this size and diversity which makes China an ideal country in which to conduct large-scale epidemiological research.

Figure 1 shows the geographic distribution of liver cancer in China. About 90% of the high mortality counties are in Guangxi, Fujan, Zhejiang and Jiangsu provinces and Shanghai. In Qidong County in Jiangsu province, for example, the death rate from liver cancer is 96.07 per 100,000 for males and 27.11 per 100,000 for females. In Qidong and adjacent counties, the highest liver cancer rates are restricted to certain adjacent communities where the land was formed from river silting of topsoil about 200 years ago (Fig. 2). Dr. Su, an epidemiologist from Shanghai, conducted several studies in 1974 and 1975. He reported that there was a strong relationship between the type of drinking water and the incidence of liver cancer (Table 1). Figure 3 shows that the risk of cancer of the liver is significantly higher for those drinking water from ditches than for those drinking well water.

If the specificity of this relationship is true, the people who stopped drinking ditch water specifically

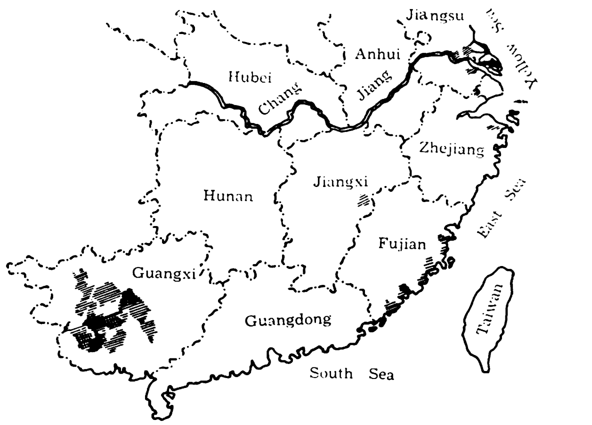

FIGURE 1. Hyperendemic areas of liver cell cancer in China.

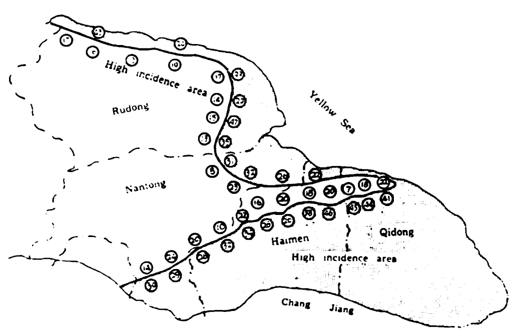

FIGURE 2. Incidence rates of liver cell cancer of boundary communes of high and low incidence areas, history of newly formed land and high incidence of liver cell cancer. Numbers in circles represent liver cell cancer mortality per 100,000 population. Shaded area represents newly formed land with a history of less than 200 years and the high incidence area.

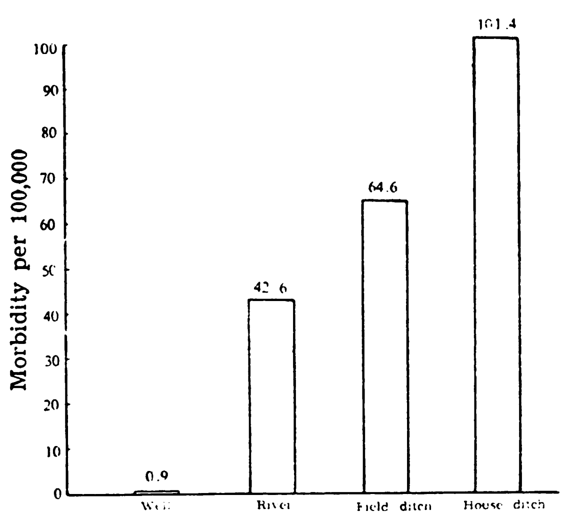

FIGURE 3. Type of drinking water and incidence of liver cell cancer; Qidong, 1971-72.

should have a decreased risk of liver cancer. In 1978 another survey was done by Shanghai First Medical College and Dr. Su. Table 2 shows the results. The percentage of consumers of different types of water has changed. Well water consumers have increased from 6% to 26%. The total mortality of liver cancer has decreased from 69.58 per 100,000 to 56.10 per 100,000, a statistically significant difference ($p = 0.0238$).

The distribution of aflatoxins in the food and hepatitis virus in the people was not nearly as strongly associated with the distribution of liver cancer as was the type of drinking water. The questions then are: Is there some kind of carcinogen in the ditch water and, if so, where does it come from? Is there some substance being washed out of the topsoil and into the ditches which is carcinogenic?

Table 3 shows the cancer mortality of four districts in the city of Peking. The highest mortality of total cancers or specifically cancers of the esophagus, stomach and liver are in Chuanwan district. The health authorities of Chuanwan District conducted a matched case control study investigating the total cases of cancer deaths. They collected data on human factors such as smoking and diet, and data on air pollution and the water supply. They found that the concentration of nitrates in the water in Chuanwan District was higher than in adjacent districts. They also found that the water supply was of generally poor quality, especially before the Revolution, because most of the residents were poor. The quality of the water is still not very good, although the water company which supplies the water to that district has been trying to improve its quality. In order to study this complex problem, the Peking Cancer Registry has been collecting data on hydrology in the whole area of Peking. It is planning a comparative study of water sources and cancer incidence.

In Gejiu city, Yunnan province, there is a tin mine. Lung cancer is a very severe problem in this area. Almost 1200 people died of lung cancer in the past 25 years; the rate is 108 per 100,000. Among them, 90% were miners who worked in the tunnel of the mine. Compared with the death rate for the general population in Yunnan province, the death rate for tin miners was almost 35-fold higher.

Some scientists began investigating the problem in 1973. The air contaminants were analyzed. It was found that there was a very high concentration of radon. After comparing different parts of the mine, the researchers hypothesized that radon daughters were the important etiologic factor in developing lung cancer. It was also discovered that the residents in Gejiu city had a 10-fold higher

Table 1. Type of drinking water and number of liver cancer cases, Qidong 1971 and 1972.

Type of drinking water	Consumers	Cases of liver cancer	Incidence per 100,000 per year
House ditch water	28,614	58	101.35
Field ditch water	37,941	49	64.57
River water	11,727	10	42.64
Well water	5,978	0	0
Total	84,080	117	69.58

Table 2. Comparison of type of drinking water and number of liver cancer cases during 2 periods, 1972-1973 and 1974-1978.

	Period 1 (1972-1973)					Period 2 (1974-1978)				
	Persons surveyed			Avg. number of cases per 100,000 per year		Persons surveyed			Avg. number of cases per 100,000 per year	
Type of drinking water	No.	%	Cases			No.	%	Cases		
House ditch	28,614	34.0	58	101.351	80.39	21,237	24.2	100	94.18	90.77
Field ditch	37,941	45.1	49	64.57		26,356	30.0	116	88.03	
River	11,727	14.0	10	42.64		16,912	19.2	30	35.48	
Well	5,798	6.9	0	0		23,415	26.6	1	0.85	
Total	84,808	100.0	117	69.58		87,920	100.0	247	56.19	

Table 3. Cancer mortality in four districts in the city of Peking, 1973-1976.

		Death rate per 100,000			
District	Total cancers	Esophageal cancers	Lung cancers	Stomach cancers	Liver cancers
Chuanwan	83.37	12.66	14.60	15.54	12.16
Xiuanwu	77.79	12.29	14.46	12.08	10.46
Xichen	73.31	9.70	11.30	12.64	9.00
Dongchen	73.92	9.53	15.00	11.30	7.79

mortality from lung cancer than the general population in Yunnan province. Which agent or agents were responsible for this elevated rate? Most of the residents in the city were related to the miners. Perhaps the miners brought some dust home, thus exposing their relatives.

Besides radon, some researchers have suspected another agent, arsenic. For a long time there was a lack of water in the Gejiu tin mine area. Miners and residents had to drink water which had been used for washing the mineral ore. This ore contained arsenic. The contaminated drinking water had arsenic at about 0.2 mg/L or more. Some waste water containing arsenic was discharged into the Gejiu Lake which had been used as drinking water by the residents until 1963. It was noted that the people living in the arsenic-polluted area had much higher death rates for lung cancer. They also had a high incidence of skin hyperkeratosis. Almost all patients with moderate or severe keratosis had a history of drinking the contaminated water in early years. Does arsenic take a part in developing lung cancer there? We really do not know. We are going to find out.

A Prospective Study Planned for China

In 1980, a group of medical researchers, who came from several major provinces to the China Cancer Control Office in Peking, discussed the possibility of doing a prospective study of cancer incidence in 5 million people. Dr. Li Ping, the Chairman of the Cancer Control Office, agreed to carry out this study and asked help from the American Cancer Society. Right now we are working on the tentative plan. Since the plan is not fully developed I will just give you a simple picture of the study.

Besides Taiwan there are 29 provinces, municipalities, and autonomous regions in China which are further divided into about 2392 counties. Because China is a huge country with varying climate and geography, with more than 50 races, and with wide variations in cancer incidence, we have the basic conditions to carry on such prospective study.

In addition to this, there is a nationwide medical network and a district resident registry system that is very complete. Each family has its own registry book, kept by the registry office where it lives, which contains the names of all family members, their ages, birthdays and birthplaces, and so on. For every child born, his or her parents must report to the registry station in order to get coupons for food and clothes. Whenever a family is going to move to another place, even to a different district in the same city, they must tell the officer in the registry station so that the family registry book will be sent to the place where they are moving. Besides, more than 80% of the people are peasants. Most of them stay in the same place for their entire lives, making complete medical follow-up possible. Since peasants live in the same place for a long time, many environmental exposures are relatively fixed.

We are going to select 2500 people who are over 40 years of age randomly from each county. In some areas, however, like Qidong and Gejiu, with special environmental problems, we will ask additional questions about some environmental factors and follow the whole population. The total number of subjects will be about 5,000,000.

Because there is some illiteracy in parts of rural China, especially among older people, we are going to interview all the subjects instead of using questionnaires. The interviews will be done either by barefoot doctors or schoolteachers. We will hold classes to train the interviewers in each locality. We hope that the questionnaire can be designed to be read by photoscanning machines.

The subjects will be divided into two groups randomly. One group will receive a physical examination at the county hospital after the first interview. The other group will only be interviewed. Then all subjects will be followed for at least ten years. They will be reinterviewed every two years. This will give us the opportunity to consider some additional questions that might come up unexpectedly as the study proceeds. All deaths will be recorded and coded according to international rules. One of the reasons we are doing the medical examination is that we will then be able to determine whether or not medical screening examinations have significantly influenced the death rate, and if these screenings are cost effective.

We are not concerned only with cancer. We will be getting data on all causes of death as they relate to a broad range of environmental and personal factors such as smoking habits and contaminated water. We believe that by cooperating with foreign scientists harmoniously, we will be able to make contributions not only to the Chinese people, but also to the entire world population.